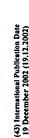
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(54) Title: SOMATOSTATIN-DOPAMINE CHIMERIC ANALOGS

(57) Abstract: Discissed is a series of somatostatin-dopamine chimeric analogs which retain both somatostatin and dopamine ac-torty in who. An example is : 6-n-propyl-8β-ergolingimethylthioacetyl-D-Pta-c-(Cya-Tyr-D-Typ-Lyp-Aba-Cyy)-Th-Miş

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## SOMATOSTATIN-DOPAMINE CHIMERIC ANALOGS

#### BACKGROUND OF THE INVENTION

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The present invention is drawn to somatostatin-dopamine chimeric analogs.

Cancer Treat. Rep. 63, 991-997 (1979); Wick, M.M., Cancer Res. 40, 1414-1418 (1980); Wick, M.M., Cancer Treat. Rep. 65, 861–867 (1981); Wick, M.M. & Mul, J. Natl. Cancer Inst. 66, 351-354 (1981); Dasgupta, et al., J. Cancer Res. Clin. Oncol. 113, 363-368 (1987); Basu, et al., Endocrine 12, 237-241 (2000); Basu, et al., J. dopamine receptors on endothelial cells. Riccl, et al., J. Auton. Phamacol.,14, 61-68 Dopamine is a catecholamine neurotransmitter that has been implicated in the Neural, 53, 17-29 (1990); Goldstein, et al., FASEB J. 6, 2413-2421 (1992); Olanow, et al., Annu. Rev. Neurosd. 22, 123-144 (1999). Egan, et al., Curr. Opin. Neurobiol. 7, 701-707 (1997). Dopamine and related molecules have been shown to inhibit the growth of several types of malignant tumors in mice, and this activity has been variously attributed to inhibition of tumor-cell proliferation, stimulation of tumor immunity or effects on melanin metabolism in malignant melanomas. Wick, M.M., J. Invest, Dermatol. 71, 163–164 (1978); Wick, M.M., J. Natl. Cancer Inst. 63, 1465–1467 (1979); Wick, M.M., Neuroimmunol. 102, 113-124 (2000). Recent studies demonstrated the presence of D2 (1994); Bacic, et al., J. Neurochem. 57, 1774-1780 (1991). Dopamine has recently been reported to strongly and selectively inhibit at non-toxic levels the vascular pathogenesis of both Parkinson disease and schizophrenia. Graybiel, et al., Adv. permeabilizing and anglogenic activities of VPF/VEGF. Basu et al., Nat. Med. 7 (5), ន 2 2

have been characterized (SSTR1 - SSTR5) (Reubl JC, et al., Cancer Res 47: 551 distribution in various tissues. Somatostatin binds to the five distinct receptor (SSTR) shown to have potent inhibitory effects on various secretory processes in tissues such as phultary, pancreas and gastrointestinal tract. SS also acts as a neuromodulator in the central nervous system. These biological effects of SS, all inhibitory in nature, are elicited through a series of G protein coupled receptors, of which five different subtypes 558, Reisine T, et al., Endocrine Review 16: 427 - 442, Lamberts SW, et al., Endocr Rev 12: 450 – 482, 4 Patei YC, 1999 Front Neuroendocrinology 20: 157 – 198). These five subtypes have similar affinities for the endogenous SS ligands but have differing Somatostatin (SS), a tetradecapeptide discovered by Brazeau et al., has been subtypes with relatively high and equal affinity for each subtype. 569-574 (2001). ង 유 32

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There is evidence that SS regulates cell proliferation by arresting cell growth via SSTR1, 2, 4, and 5 subtypes (Buscail L, et al., 1995 Proc Natl Acad Sci USA 92: 1580 – 1584; Buscail L, et al., 1994 Proc Natl Acad Sci USA 91: 2315 – 2319; Florio T, et al., 1999 Mol Endocrinol 13: 24 – 37; Sherma K, et al., 1999 Mol Endocrinol 13: 82 – 90), or by inducing apoptosis via SSTR3 subtype (Sharma K, et al., 1996 Mol Endocrinol 10: 1688 – 1696). SS and various analogues have been shown to inhibit normal and neoplastic cell proliferation in vitro and vivo (Lamberts SW, et al., 1996 Mol Endocrinol 10: 450 – 482) via specific SS receptors (SSTR's) (Patel YC, 1999 Front Neuroendocrinology 20: 157 – 198) and possibly different postreceptor actions (Weckbecker G, et al., Pharmacol Ther 60: 245 - 264; Bell Gl, Reisine T 1993 Trends Neurosci 16: 34 – 38; Patel YC, et al., Biochem Biophys Res Commun 198: 605 – 612; Law SF, et al., Cell Signal 7:1 – 8). In addition, there is evidence that distinct SSTR subtypes are expressed in normal and neoplastic human tissues (9), conferring different tissue affinities for various SS analogues and variable clinical response to their therapeutic effects.

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inhibition of insulin and/or glucagon for treating diabetes mellitus, angiopathy, type-5 receptor ("SSTR5") (Coy, et al. 197:366-371 (1993)). Activation of types 2 and 5 biological response, thus, reducing interaction with other receptor subtypes which could chronic pancreatitis and gastrointestinal hormone secreting tumors; treatment of cancer have been associated with growth hormone suppression and more particularly GH (Raynor, et al., Molecular Pharmacol. 43:838 (1993); Lloyd, et al., Am. J. Physiol associated with the treatment of various conditions and/or diseases. ("SSTR2") and gastrointestinel bleeding. It is preferred to have an analog which is selective for the as arthritis; retinopathy; chronic allograft rejection; angioplasty; preventing graft vessel such as hepatoma; inhibition of anglogenesis; treatment of inflammatory disorders such secretion and more particularly peptic ulcers, proliferative retinopathy, dawn phenomenon and nephropathy, inhibition of gastric acid indications associated with activation of the somatostatin receptor subtypes include but not type 5 has been associated with treating prolactin secreting adenomas. Other secreting adenomas (Acromegaly) and TSH secreting adenomas. Activation of type 2 258:G102 (1995)) while the inhibition of insulin has been attributed to the somatostatin specific somatostatin receptor subtype or subtypes responsible for the desired diarrhea syndrome, AIDS related diarrhea, chemotherapy-induced diarrhea, acute or pancreaticocutaneous fistula, irritable bowel syndrome, Dumping syndrome, watery Binding to the different types of somatostatin receptor subtypes have been enterocutaneous and

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lead to undesirable side effects.

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Somatostatin (SS) and its receptors (SSTR1 to SSTR5) are expressed in normal human parafollicular C cells and meduliary thyroid carcinoma (MTC). MTC is a tumor originating from thyroid parafollicular C cells that produces calcitonin (CT), somatostatin, as well as several other peptides (Moreau JP, et al., Metabolism 45 (8 Suppl 1): 24 – 26). Recently, Mato et al. showed that SS and SSTR's are expressed in human MTC (Mato E, et al., J Clin Endocrinol Metab 83: 2417 – 2420). It has been documented that SS and its analogues induce a decrease in plasma CT levels and a symptomatic improvement in MTC patients. However, until now the antiproliferative activity of SS analogues on tumor cells had not been clearly demonstrated (Mahler C, et al., Clin Endocrinol 33: 261-9; Lupoil G, et al., Cancer 78: 1114 – 8; Smid WM, et al., Neth J Med 40: 240 – 243). Thus, development and assessment of SSTR subtype analogues selective on MTC cell growth provides a useful tool for clinical application. Until now, no data concerning specific SSTR subtype involvement in MTC cell growth regulation have been reported.

#### SUMMARY OF THE INVENTION

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The present invention is concerned with the discovery of a series of somatostatin-dopamine chimeric analogs that retain both somatostatin and dopamine activity in vivo, including several of which display enhanced biological activity over the native somatostatin and dopamine analogs alone, and the therapeutic uses thereof.

In one aspect the invention features a dopamine-somatostatin chimer of formula

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wherein:

25 X is H, Cl, Br, I, F, -CN, , or C<sub>1.8</sub> alkyl;

R1 is H, C14 alkyl, allyl, alkenyl or -CN;

R2 and R3, each are, independently H or absent, provided that when R2 and R3 are absent a double bond is present between the carbon atoms to which they are attached; R4 is H or -CH<sub>3</sub>;

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Y is -O., -C(O)-, .S., S.(CH3)s-C(O)-, -S(O)-, -S(O)-, -SC(O)-, -OC(O)-, -N(R5)-C(O)-,

or -N(R8)-;

R5, R6, R7 and R8 each is, independently, H or C₁₂ alkyl;

R8 is H or C<sub>1-6</sub> alkyl;

m ls 0 or 1;

n is 0-10;

L is {CH<sub>2</sub>}p-C(O)-, when Y is -S-, -S(O)-, -S(O)<sub>2</sub>-, -O- or -N(R6)-;

L is -C(O)-(CR7R8)q-C(O)-, when Y is -N(R6)-, -O-, or -S-;

L is -{Doc)t-, when Y is -C(O)-, SC(O)-, -OC(O)-, -S-(CH2)s-C(O)-, or -N(R5)-C(O)-;

p ls 1-10; 2

s Is 1-10; q ls 2-4;

tis 1-10; and

or a pharmaceutically acceptable salt thereof. Z is somatostatin analog,

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In another aspect the invention features a dopamine-somatostatin chimer of formula (II),

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wherein: 2 X Is H, CI, Br, I, F, -CN, , or C, a alkyl;

R1 is C1-4 alkyl, H, allyl, alkenyl or -CN;

R2 and R3, each are, independently H or absent, provided that when R2 and R3 are absent a double bond is present between the carbon atoms to which they are attached;

R4 is H or -CH3;

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R5 is C1-5 alkyl group, or a group of the formula of -(CH2)rN(CH3)q;

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Y is -O., -C(O)-, .S., -SC(O)-, -OC(O)-, -N(R6)-C(O)-, -N(R7)-, or -N(R8)-(CH2)8-C(O)-; R6, R7, R8, R9 and R10 each is, independently, H or C₁₂ alkyl;

L is -(CH2)p-C(O)-, when Y is -S-, -O- or -N(R7)-;

L is -C(O)-(CR9R10)q-C(O)-, when Y is -N(R7)-, -O-, or -S-;

L is -{Doc)t-, when Y is -C(O)-, SC(O)-, -OC(O)-, -N(R8)-(CH2)s-C(O)-, or -N(R8)-C(O)s

m is 0 or 1;

n ls 2-10;

ris 1-8,;

q ls 2-4;

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p is 1-10;

s ls 1-10;

t ls 1-10; and

Z is somatostatin analog

or a pharmaceutically acceptable salt thereof.

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In one embodiment the Invention features a compound according to the formula:

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D-Phe-cyclo(Cys-Phe-D-Trp-Lys-Thr-Cys)-Thr-ol

\_(Doc)<sub>3</sub>-D-Phe-cyclo[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-ol

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H (Dock-Lys-D-Tyr-D-Tyr-cyclo(Os-Pha-D-Trp-Lys-Thr-Oss)-Thr-NHs, H (Dock the D-Tim D-Tim cyclo(Ose Phe D-Tim the Tim Ose)-Tim AHs DooNb-D-Tyr-D-Ser-cyclo[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-NH<sub>2</sub> \_\_\_S\_\_(D-Ser)<sub>k</sub>NIe-D-Tyr-D-Ser-cyclo(c)a-Pha-D-Trp-Lya-Thr-Oya)-Thr-NH-<sub>k</sub> 0 ~S∕\\\\\(D\$ss)<sub>nd</sub>Lys-DTyr-O-Tyr-Oycb(Oys-Pho-DTpD-Lys-Thr-Oys}-Thr-NH<sub>s</sub> (Doc);-D-Phe-cyclo(Oys-Tyr-D-Trp-Lys-Abu-Oys)-Thr-NH<sub>2</sub> ╱(D-Set)<sub>6</sub>-Lys-D-Tyr-D-Tyr-cyclo[Cys-Pho-D-Trp-Lys-Thr-Cys}-Thr-NH<sub>2</sub>

H (Dock-D-Phe-sydolOse-Tyr-D-Trp-Lise-Val-Oss)-Trp-NH-

D-Phe-cyclo(Cys-Tyr-D-Trp-Lys-Val-Cys)-Trp-NH<sub>2</sub>

\_\_s\_\_bocNie-D-Tyr-D-Ser-cycb[Oye-Tyr-D-Trp-Lye-Val-Oye]-Trp-NH<sub>2</sub>

S (Doc)z-Lya-D-Tyr-D-Tyr-cyclo(Cya-Tyr-D-Typ-Lya-Val-Cya)-Typ-NH<sub>2</sub> ~S (Doc)3-Lys-D-Tyr-D-Tyr-cyclo(Cys-Tyr-D-Trp-Lys-Vel-Cys-Trp-NH<sub>2</sub>

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Caeg = N-(2-aminoethyl)-N-(2-cytoslnyl-1-oxo-ethyl)-glycine

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~s∕r (Doc)₃-cydo(Cys-Phe-Tyr-D-Tpp-Lys-Thr-Phe-Cys]-NH₂ O Cycb[Os-Pho-Tyr-D-Tyr-Os-Thr-Pho-Cys]-NH2 S Codd(Cor-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys)-NH-, --- D-Nat-cyclo[Cya-Tyr-D-Trp-Lya-Vat-Cya]-Thr-NH<sub>2</sub> Ser-cydo[Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys]-NH<sub>2</sub>

M—(Doc),-D-Phe-cyclo(Cye-Tyr-D-Trp-Lya-Abb-Cya)-Thr-NH-Dood-Phe-cyclo(Oye-Tyr-D-Trp-Lys-Abu-Oys)-Thr-NH<sub>3</sub> Dock-D-Pho-cycle(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH2 L\_D-Phe-cyclo(Cye-(3-Bromo-Tyr)-D-Trp-Lys-Thr-Cys)-Thr-NH<sub>2</sub> L\_(Dac),-Lya-D-Tyr-O-Tyr-cyclo(Cya-Pha-O-Typ-Lya-Thr-Cys)-Thr-NH,

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-(Doc),-Lye-D-Tyr-D-Tyr-cyclo(Cya-Phe-D-Trp-Lye-Thr-Cya)-Thr-NH-

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-D-Phe-cyclc(Cye-Tyr-D-Trp-Lye-Abu-Cys)-Thr-NH<sub>2</sub>

H COSMINALISED TWO TWO INCIDENCE TRANSPIRABLE

— (D-Ser), NIO-D-Ty-D-Ser-cycld(C)a-Pha-D-Trp-Lya-Thr-Cys)-Thr-NH,

H COSeracte-O-Tyro-Tyropide(O,e-Pre-O-Tre-Cyr)-T

— D-Nat-cyclo(Cya-Tyr-D-Trp-Lya-Vot-Cya)-Thr-Nth

Occi, Octhe cycle(Cys-Tyr-O-Trp-Lys-Abu-Cys)-The-NH<sub>1</sub>



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H Democratica-Pra-D-Trp-Lya-Thr-Ops)-Threa HA Dock-D-Phe-cyclo(Dye-Phe-D-Trp-Lye-Thr-Oye)-Thr-d Description Tyropadicy TyroTranspare Valoria Transparent HA D Senty-New-D-Ty-D-Senty-play-Ty-D-Trip-Lye-Visi-Oye)-Trp-NHy H Delinociation-Ty-D-Trp4, water Only-Trp484,

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-Doo-Nie-O-Ty-D-Ser-cyclo(Cye-Tyr-D-Trp-Lye-Val-Cye)-Trp-NH<sub>2</sub>

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HA DSenh-Lyn-DTyr-Ozfot(Ope-Pine-DTipsLyn-Tin-Ope)-Tin-Nils,

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D-Pha-cyclo(Cya-Tyr-D-Trp-Lya-Val-Cya)-Trp-NH-

(Doo),-D-I'ne-cyclo(Cye-Tyr-D-Trp-Lye-Va;-Oye)-Trp-NH,

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HN (D-Ser)<sub>N</sub>-Lye-D-Tyr-Oyd-Oye-Tyr-O-Top-Lye-Val-Oel-Trp-NH<sub>2</sub>.

Compound E HAT (Dock-Line D-Tine Open Conference Tine D-Tine Open Conference Tine New York Conference New York Confer H LOSery-Neo-Ty-O-Ser-cycle(Ope Ty-O-Top-Lys-Arth-Ope)-Top-Net-, D-Nai-cyclo(Cys-Tyr-D-Trp-Lys-Vai-Cys)-Thr-NH<sub>2</sub> D-Phe-cyclo(Gys-Tyn-D-Trp-Lys-Tin-Gys)-Nai-NH-

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D-Phe-sycht(Cye-(3-Brame-Tyr)-D-Trp-Lye-Thr-Cys)-Thr-Wy,

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HH (DOU), Define cycle(Ope Tyr.D-Trp.Lye-Abu-Cypl-Trr-WH,

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(D-Serg-Lya-O-Tyn-O-Tyn-cycle(Cya-Pha-O-Typ-Lya-Thr-Cya)-Thr-d

Lys-D-Tyr-D-Tyr-cycld(Oys-Pho-O-Trp-Lys-Thr-Cys)-Thr-ci

Dacy-Dens-cycla(Cys-Pho-O-Try-Lys-Thr-Cys)-Thr-d Doo-D-Pha-cyclo(D)a-Pha-D-Trp-Lya-Thr-Oyal-Thr-cl (Doc),-D-Pha-cyclo(Cya-Pha-D-Trp-Lya-Thr-Cya)-Thr-ol O. Nia-D-Tyr-D-Ser-cystq(Cya-Pha-D-Trp-Lya-Thy-Cya)-Thr-d Lys-D-Tyr-O-Tyr-cydd(Cys-Pho-O-Trp-Lys-Thr-Cys)-Thr-d L\_AEPA-D-Pho-cycle(Cys-Pho-D-Try-Lys-Thr-Cys)-Thr-d 

H AEPAO-Pte-cydd(Oje-Pte-O-Try-Lys-Thr-Oje)-Thr-d H (D.Sarjed.ya-D.Tyr-D.Tyr-cycldCya-Pha-D.Trpd.ya-Thr-Oja)-Thr-d (Doc), D-Phe-cyclo(Cyn-Phe-D-Trp-Lyn-Thr-Cyn)-Thr-ci Doo-D-Phe-cycld(Cye-Phe-D-Trp-Lye-Thr-Cye)-Thr-cl — Doc-Na-D-Tyr-O-Ser-cyclo(Cys-Pho-O-Trp-Lys-Thr-Gys)-Thr-di

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√(Doc)3-D-Pha-cyclq(Oya-Pha-D-Trp-Lya-Val-Cya}-Thr-NH,

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P CCH, I DOCO Phe cyclope Phe D Top Lye Val Cys) Thr ANH, H N CO-Seng-Lya-DTys-O-Tys-cycle(Cya-Pha-D-Try-Lya-Via-Cya)-Thr-NH-I, ~S Doot, ye DTyr OTyr cydd(Oye Phe O-Trpt, ye Vis Oys)-Thrithir O

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/Aepa-D-Phe-cyclo[Cye-(3-lodo-Tyr)-D-Trp-Lys-Vel-Cys]-Thr-NH<sub>2</sub>

∠D-Pha-cyclo(Cya-(3-lodo-Tyr)-D-Trp-Lya-Val-Cys[-Thr-NH<sub>2</sub>

(Doc), Aepa-Lys-OTyr-D-Tyr-cydo[Cys-Tyr-D-Trp-Lys-Abu-Cys|-Thr-Nth, /\_(Doc)<sub>3</sub>-Aepa-Lya-DTyr-D-Tyr-oydo(Cya-Tyr-D-Trp-Lya-Abu-Cys)-Thr-NH<sub>2</sub> //(Doch-Aepa-Lya-DTyr-D-Tyr-cyclo(Cya-Tyr-D-Trp-Lya-Abu-Cys)-Tir-NH<sub>2</sub> /Aepa-Lya-DTyr-D-Tyr-cyclo[Cys-Tyr-D-Trp-Lya-Abu-Cys]-Thr-NH<sub>2</sub> /Lya-DTyr-D-Tyr-cydo(Cya-Tyr-D-Trp-Lya-Abu-Cya)-Thr-NH<sub>2</sub> ∠Doo-Aepa-Lys-DT)r-D-Tyr-cyclo(Cya-Tyr-D-Trp-Lys-Abu-Cysj-Thr-NH<sub>z</sub> ,(Doc)<sub>z</sub>-(Aspa)<sub>z</sub>-Lys-DTyr-D-Tyr-cydo[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>z</sub> ,(Doc)<sub>t</sub>-Aepe-Lys-DTyr-D-Tyr-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Tir-NH<sub>z</sub> \_(Doc)<sub>z</sub>-Aepa-Lya-DTyr-D-Tyr-cydo(Cya-Tyr-D-Trp-Lya-Abu-Cys]-Thr-NH<sub>2</sub> ^epa)<sub>z</sub>-D-Phe-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys}-Thr-NH<sub>2</sub>

/(Doc),-Aepa-D-Pho-cyclo(Cye-(3-lodo-Tyr)-D-Trp-Lye-Val-Cys)-Thr-NH<sub>2</sub>

<(Doc)<sub>2</sub>-Aspa-D-Phe-cyclo[Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Cys}-Thr-NH<sub>2</sub>

.epa-D-Pha-cydo(Cya-(3-lodo-Tyr)-D-Trp-Lys-Val-Cys)-Thr-NH2

∠Doc-D-Phe-cydo(Cys-(3-lodo-Tyr)-D-Trp-Lys-Vsl-Cysj-Thr-NH<sub>2</sub>

ر(Doc),-D-Phe-cydo(Cys-(3-lodo-Tyr)-D-Trp-Lys-Vai-Cys}-Trr-NH<sub>2</sub>

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∠(Doc)<sub>3</sub>-D-Pho-cyclo[Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Cys}-Thr-NH<sub>3</sub>

/(Doc)<sub>2</sub>-D-Pha-cydo(Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Cys)-Thr-NH<sub>2</sub>

/Aspa-D-Nat-cyclo(Cys-Tyr-D-Trp-Lys-Val-Cys)-Thr-NH 2

-Aepa-D-Pha-cydo[Cys-Tyr-D-Trp-Lya-Thr-Cys]-Nai-NH

-Aepa-D-Phe-cydo(Cys-Phe-D-Trp-Lys-Thr-Cys)-Thr-ol

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(Doc)2-Aepa-D-Phe-cyclo[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH

(Aeps),-DPNe-cycl(Cye-Tyr-D-Trp-Lye-Abu-Cys}-Thr-NH 2

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S DOO Aagaa D.Phia cyclo(Cya-Tyr.D.Trp-Lya-Abu-Cya)-Thr-NH <sub>s</sub>

S Agga-DPN-0,00(0,9-1)r-D-TD-Lys-Abu-Oys-Thr-NH 3

S (Doc), DPhe cydolC/0=Tyr.D-Trp.Lys-Abu-Cys)-ThraMH a

S Dood Phecydol Ope Tyr. D Tro Lya-Azu-Cys) Thr-NH 1

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(Actor) D-Phe-cyclol Oye-Tyr-D-Trp-Lys-Abu-Cys)-Thi-NH 0

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/Aspe-D-Phe-cydc[Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Cys]-Thr-NH<sub>2</sub>

HILL S DEPRENCIACIONS (3-lodo-Tyr)-D-Trp-Lys-Val-Oys)-Thr-NH<sub>2</sub>

HILL S DOOALESS-D-Phe-cyclo(Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Oys)-Thr-NH<sub>3</sub>

HILL S DOOALESS-D-Phe-cyclo(Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Oys)-Thr-NH<sub>3</sub>

HILL S DOOD-D-Phe-cyclo(Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Oys)-Thr-NH<sub>3</sub>

HILL S DOOD-D-Phe-cyclo(Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Oys)-Thr-NH<sub>3</sub>

HILL S DOOD-D-Phe-cyclo(Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Oys)-Thr-NH<sub>4</sub>

HN S (Doc)<sub>k</sub>-Lys-DTyr-D-Tyr-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>3</sub>
HN S (Doc)<sub>k</sub>-Lys-DTyr-D-Tyr-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>3</sub>
HN S (Doc)<sub>k</sub>-Lys-DTyr-D-Tyr-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>3</sub>
HN S (Doc)<sub>k</sub>-Lys-DTyr-D-Tyr-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>4</sub>

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/ Doot ya-DTyr-D-Tyr-cydo[Cya-Tyr-D-Trp-Lya-Abu-Cya]-Thr-NH<sub>2</sub>

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~S (Doc)<sub>2</sub>-Lye-DTyr-D-Tyr-cydd(Cye-Tyr-D-Trp-Lye-Aby-Cys)-Thr-NH<sub>2</sub>

-S (Doc),-Lya-D1yr-D-Tyr-cydolCya-Tyr-D-Trp-Lya-Abu-Cya)-Thr-NH<sub>2</sub>

.S (Doc)<sub>2</sub>-Lye-DTyn-D-Tyn-cydolOye-Tyn-D-Trp-Lye-Abu-Cys)-Thin-NH<sub>2</sub>

(Doc), Lya-DTyr-D-Tyr-cyclo[Cya-Tyr-D-Trp-Lya-Abu-Cys]-Thr-NH,

(Doc),-Lya-DTyn-D-Tyn-cydo[C)s-Tyn-D-Trp-Lya-Abu-Cyaj-Thr-NH<sub>2</sub>

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∠(Doc)<sub>3</sub>-D-Pha-cyclo[Cys-Tyr-D-Trp-Lys-Abu-Cys}-Thr-NH<sub>2</sub>

\DocAepa-D-Phe-cydo[Oys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>2</sub> D-Phe-cyclo[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>2</sub> Doc-D-Phe-cyclo[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>2</sub> \D-Phe-cydo[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>2</sub> \(Doc)<sub>e</sub>-Aepa-D-Phe-cyde[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>2</sub> \(Doc)<sub>z</sub>-Aepa-D-Phe-cydo[Cys-Tyr-D-Trp-Lys-Abu-Cys}-Trr-NH<sub>2</sub> `(Aepa)<sub>z</sub>-D-Phe-cydo[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>2</sub> Aapa-D-Phe-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>2</sub> Aepa-D-Pha-cyclo[Cys-Tyr-D-Trp-Lys-Thr-Cys]-Nal-NH<sub>2</sub> Aspa-D-Pho-cyclo[Cys-Pho-D-Trp-Lys-Thr-Cys]-Thr-ol Aspa-D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2

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N (Dock, 4/8 400), 4/8 - DTyr-D-Tyr-Ordo[Cya-Tyr-D-Tyr

""" (Docs, Appelye DIYA-D-Tyr-cyddicye Tyr-C-Tyr-Lye Aby-Cyst Thr-NY

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"" (1000), Adapadaya DTyr. Dycholopa Tyr. D. Tyr. 1904(Dya Tyr. D. Tyr. 1904), Thr. 444,

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H, N, N (Doc), Lya-DTyr-D-Tyr-cydolCya-Tyr-D-Trp-Lya-Abu-Cya)-Trr-NH,

CDoc), Lys-DTyr-D-Tyr-cydo[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH,

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S Aspe-Aspe-D-Phe-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NHy.

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Appe-Appe-D-Pine-cydd(Cye-(3-lodo-Tyy)-D-Trp-Lys-Val-Cya)-Thr-NH4
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Appe-Appe-D-Pine-cydd(Cye-1yr-D-Trp-Lys-Abu-Cys)-Thr-NH4

H Aspe-Aspe D-Phe-cydol(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub>

HA Aspendant Dens cyclo(Cys (3-lodo Tyy) D-Trp-Lys-Wal-Cys) Thr-NH1,

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HA Aspendant Dens cyclo(Cys - Tyn-D-Trp-Lys-Wal-Cys)-Thr-NH2,

HA Aspendant Cys - Tyn-D-Trp-Lys-Abu-Cys)-Thr-NH2,

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Aspe-Aspe-D-Phe-cyclo(Cye-(3-lodo-Tyy)-D-Trp-Lye-Val-Cye)-Trr-Lyth-

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or a pharmaceutically acceptable salt thereof.

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In one aspect the invention features a method of eliciting a dopamine receptor agontst effect in a subject in need thereof, wherein said method comprises administering to said subject an effective amount of a compound according to formula (I) or formula (II), or a pharmaceutically acceptable salt thereof. In a preferred embodiment of this aspect the compound is selected from among the compounds

In another aspect the invention features a method of eliciting a somatostatin receptor agonist effect in a subject in need thereof, wherein said method comprises administering to said subject an effective amount of a compound according to formula (I) or formula (II), or a pharmaceutically acceptable sait thereof. In a preferred embodiment of this aspect the compound is selected from among the compounds specifically disclosed herein.

In another aspect the invention features a method of simultaneously eliciting both a dopamine receptor agonist effect and a somatostatin receptor agonist effect in a subject in need thereof, wherein said method comprises administering to said subject an effective amount of a compound according to formula (I) or formula (II), or a pharmaceutically ecceptable sait thereof. In a preferred embodiment of this aspect the compound is selected from among the compounds specifically disclosed herein.

In another aspect the Invention features a pharmaceutical composition comprising an effective amount of a compound according to formula (I) or formula (II), or a pharmaceutically acceptable saft thereof, and a pharmaceutically acceptable carrier. In a preferred embodiment of this aspect the compound is selected from among the compounds specifically disclosed herein.

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In another espect the invention features a method of treating a disease or condition in a subject, said method comprising administering to said subject a therapeutically effective amount of a compound of formula (1) or formula (11), or a pharmaceutically exceptable sait thereof, wherein said disease is selected from the list consisting of lung cancer, glioma, anorexia, hypothyroidism, hyperaldosteronism, H. pylori proliferation, acromegaly, restenceis, Crohn's disease, systemic sclerosis, external and internal pancreatic pseudocysts and ascites, ViPorna, reskloblastosis, hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, diarrhea, Albox related diarrhea, chemotherapy related diarrhea, scleroderma, Inritable Bowel Syndrome, pancreatitis, small bowel obstruction, gastroesophageal reflux, duodenogastric reflux, Cushing's Syndrome, gonadotropinoma, hyperparathyroidism, Graves' Disease, diabetic neuropathy, Paget's disease, polycystic overy disease, thyroid cancer, hepertome, leukemia, meningioma, cancer cachexia, orthostatic hypotension,

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postprandial hypotension, panic attacks, GH secreting edenomas, Acromegaly, TSH secreting adenomas, prolactin secreting adenomas, linsulinoma, glucagonoma, diabetes meilitus, hyperlipidemia, insulin insensitivity. Syndrome X, angiopathy, proliferative retinopathy, dawn phenomenon, Nephropathy, gastric acid secretion, peptic ulcers, enterocutaneous fistula, pancreatiticocutaneous fistula, Dumping syndrome, watery diarrhea syndrome, pancreatitis, gastrointestinal homorie secreting tumor, angiogenesis, arthritis, allograft rejection, graft vessel bleeding, portal hypertension, gastrointestinal bleeding, obesity, and opioid overdose. In a preferred embodiment of this aspect the compound is selected from among the compounds specifically disclosed to herein, in a more preferred embodiment of this aspect of the invention said disease or

In a particularly preferred embodiment of each of the foregoing methods the compound is selected from the list of compounds consisting of Compound A through Compound K, or from among the list of compounds consisting of Example L through Example V, as disclosed hereinbelow under the heading "Synthesis of Somatostatin-

condition is acromegaly.

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Dopamine Chimers.

In another espect of the Invention is featured a dopamine agonist according the

formula (I) or formula (II), hereinabove, wherein the somatostatin analog "z" is replaced by a molety comprising -H, -OH, (C<sub>1</sub>-C<sub>6</sub>)alkoxy, anylalkoxy, (e.g., benzyl, substituted benzyl, and the like), -NH<sub>2</sub>, -NR9R10, where R9 and R10 are as defined in formula (II). In a preferred embodiment of this aspect said dopamine agonist is selected from among the dopamine molety components of the dopamine-somatostatin chimers disclosed herein, or a pharmaceutically acceptable sait thereof. In a most preferred embodiment of this aspect said dopamine agonist is:

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or a pharmaceutically acceptable salt thereof.

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### DETAILED DESCRIPTION OF THE INVENTION

utilise the present invention to its fullest extent. The following specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of It is believed that one skilled in the art can, based on the description herein, the disclosure in any was whatsoever.

same meaning as commonly understood by one of ordinary skill in the art to which this Unless defined otherwise, all technical and scientific terms used herein have the invention belongs. Also, all publications, patent applications, patents, and other references mentioned herein are incorporated by reference, each in its entirety.

- SSTR-2, SSTR-3, SSTR-4, and SSTR-5. Thus, a somatostatin agonist may be one or more of an SSTR-1 agonist, SSTR-2 agonist, SSTR-3 agonist, SSTR-4 agonist or a SSTR-5 agonist. What is meant by, e.g., a somatostatin type-2 receptor agonist (i.e., Various somatostatin receptors (SSTR's) have been Isolated, e.g., SSTR-1, SSTR-2 agonist) is a compound which has a high binding affinity (e.g., KI of less than 100 nM, or preferably less than 10 nm, or more preferably less than 1 nM) for SSTR-2 (e.g., as defined by the receptor binding assay described below). What is meant by, e.g., a somatostatin type-2 receptor selective agonist is a somatostatin type-2 receptor agonist which has a higher binding affinity (i.e., lower Ki) for SSTR-2 than for any other somatostatin receptor. 2 2
- In one embodiment the SSTR-2 agonist is also a SSTR-2 selective agonist. Examples of SSTR-2 agonists which may be used to practice the present invention include, but are not limited to:

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D-Nal-cyclo[Cys-Tyr-D-Trp-Lys-Val-Cys]-Thr-NH2;

cyclo[Tlc-Tyr-D-Trp-Lys-Abu-Phe];

4-(2-Hydroxyethyl)-1-piperazinylacetyl-D-Phe-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH2;and

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4-(2-Hydroxyethyl)-1-piperazine-2-ethanesulfonyl-D-Phe-cyclo(Cys-Tyr-D-Trp-

Further examples of somatostatin agonists are those covered by formulae or Lys-Abu-Cys)-Thr-NH2.

those specifically recited in the publications set forth below, each of which is hereby Incorporated by reference in its entirety. 8

EP Application No. P5 164 EU (Inventor: G. Kerl); Van Binst, G. et al. Peptide Research 5:8 (1992);

Horvath, A. et al. Abstract, "Conformations of Somatostatin Analogs Having

Antitumor Activity", 22nd European peptide Symposium, September 13-19, 1992,

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Intertaken, Switzerland;

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EP Application No. 0 363 589 A2 (1990); EP Application No. 0 203 031 A2 (1986); U.S. Patent No. 4,904,642 (1990); U.S. Patent No. 4,282,143 (1981); U.S. Patent No. 4,871,717 (1989); U.S. Patent No. 4,853,371 (1989); U.S. Patent No. 4,725,577 (1988); U.S. Patent No. 4,684,620 (1987); U.S. Patent No. 4,650,787 (1987); U.S. Patent No. 4,603,120 (1988); U.S. Patent No. 4,585,755 (1986); U.S. Patent No. 4,522,813 (1985); U.S. Patent No. 4,486,415 (1984); U.S. Patent No. 4,485,101 (1984); U.S. Patent No. 4,435,385 (1984); U.S. Patent No. 4,395,403 (1983); U.S. Patent No. 4,369,179 (1983); U.S. Patent No. 4,360,516 (1982); U.S. Patent No. 4,328,214 (1982); U.S. Patent No. 4,316,890 (1982); U.S. Patent No. 4,310,518 (1982); U.S. Patent No. 4,291,022 (1981); U.S. Patent No. 4,238,481 (1980); U.S. Patent No. 4,224,199 (1980); U.S. Patent No. 4,133,782 (1979); U.S. Patent No. 4,261,885 (1981); U.S. Patent No. 4,728,638 (1988); U.S. Patent No. 4,215,039 (1980); U.S. Patent No. 4,358,439 (1982); U.S. Patent No. 4,235,886 (1980); U.S. Patent No. 4,211,693 (1980); U.S. Patent No. 4,190,648 (1980); U.S. Patent No. 4,146,612 (1979); U.S. Patent No. 5,506,339 (1996); U.S. Patent No. 4,209,426 (1980); 2 2 8 ន្ត 35 ង

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EP Patent No. 0 389 180 (1990);
EP Application No. 0 505 680 (1982);
EP Application No. 0 083 305 (1982);
EP Application No. 0 083 305 (1982);
EP Application No. WO 88/05052 (1988);
PCT Application No. WO 90/12811 (1990);
PCT Application No. WO 97/01579 (1997);
PCT Application No. WO 91/18016 (1991);
U.K. Application No. GB 2,095,261 (1981); and French Application No. FR 2,522,655 (1983).

Note that for all somatostatin agonists described herein, each emino ecid residue represents the structure of -NH-C(R)H-CO-, in which R is the side chain (e.g., CH<sub>3</sub> for Ala). Lines between amino acid residues represent peptide bonds which join the amino acids. Also, where the amino acid residue is optically active, it is the L-form configuration that is intended unless D-form is expressly designated. For clarity, disurfide bonds (e.g., disulfide bridge) which exist between two free thicls of Cys residues are not shown. Abbreviations of the common amino acids are in accordance with IUPAC-IUB recommendations.

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#### Synthesis of Somatostatin Agonists

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The methods for synthesizing peptide somatostatin egonists are well documented and are within the ability of a person of ordinary skill in the art. For example, peptides are synthesized on Rink amide MBHA resin (4-(2'4'-dimethoxyphenyl-Fmoc-aminomethyl)-phenoxyacetamido-norieucyl-MBHA resin) using a standard solid phase protocol of Fmoc chemistry. The peptide-resin with free amino functional at the N-terminus is then treated with the corresponding compound containing doparnine molety. The final product is cleaved off from resin with TFA/water/triisopropy/silane (TIS) mbbure.

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For example, synthesis of H-D-Phe-Phe-Phe-D-Trp-Lys-Thr-Phe-Thr-NH<sub>6</sub>, can be achieved by following the protocol set forth in Example i of European Patent Application 0 395 417 A1. The synthesis of somatostatin agonists with a substituted N-terminus can be achieved, for example, by following the protocol set forth in PCT Publication No. WO 88/02756, PCT Publication No. WO 94/04752, and/or European Patent Application No. 0 329 295.

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Peptides can be and were cyclized by using todine solution in MeOH/water and purified on C18 reverse-phase prep. HPLC, using acetonitrile-0.1%TFA/water-0.1%TFA

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buffers. Homogeneity was assessed by analytical HPLC and mass spectrometry and determined to be >85% for each peptide.

Certain uncommon amino acids were purchased from the following vendors: Fmoc-Doc-OH and Fmoc-AEPA were purchased from Chern-Impex International, Inc. (Wood Dale, IL, USA), Fmoc-Caeg(Bhoc)-OH was purchased from PerSeptive Biosystems (Framingham MA, USA), Bhoc stands for benzhydryfoxycarbonyf.

#### Synthesis of Dopamine Agenists

The methods for synthesizing many dopamine agonists are also well documented and are within the ability of a person of ordinary skill in the art. Further synthetic procedures are provided in the following reaction schemes and examples.

cheme 1

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oxidation

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Scheme11:

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1) BrCH<sub>2</sub>C(O)OBzl/Base. 2) [ H ]

1) Br(CH),-CO,B22 2) [ H ]

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Similarly for compounds 6, 7 and 8:

Similarly for compounds 6, 7 and 8:

2 H3(CH<sub>2</sub>CO<sub>2</sub>AR)

1 OH

2 H3(CH<sub>2</sub>CO<sub>2</sub>AR)

4 H

1 OH

2 H3(CH<sub>2</sub>CO<sub>2</sub>AR)

(I)

Similarly for compounds 6, 7 and 8:

(I)

Similarly for compounds 6, 7 and 8:

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Where R" and R" are, independently, H or C, -C, alkyl

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R" N=C=N (CH<sub>2</sub>), N-R"

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1. Ms CL-pyridine 2.

3. NH<sub>2</sub>-NH<sub>2</sub>-H<sub>2</sub>0

1. Coupiing

сн,и, со(сн,),-со,н

1. Coupling

Scheme III

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CH\_NH CO (CH<sub>2</sub>)<sub>p</sub>-Somatostatin/Derivative

DeBlocking

Scheme V

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N, N'-disuccinimidyl carbonate

### Scheme VI

## Synthesis of Somatostatin-Doparnine Chimers

The somatostath-dopamine chimers may be synthesized according to the following reaction schemes and examples. Starting material and intermediates for compounds (I), (II) and (III), depicted in Scheme I, II, and III, respectively, are commercially available or prepared by the literatures; Pharmazie 39, 537 (1984); collect Czech. Chem. Commun. 33, 577 (1986); Helv. Chim. Acta 32, 1947, (1949) U.S.P. 5,097,031; USP 3,901,894; EP 0003657; USP 4,526,892. The synthesis of peptides are within the scope of a skilled person in the art, and in any event, is readily available in the literature. See, e.g., Stewart et al., Solid Phase Synthesis, Pierce Chemical. 2<sup>rd</sup> Ed. 1984; G.A. Grant; Synthetic peptide. WH., Freenand Co., New York, 1992; M. Bodenszky A. Bodenszky, The Practice of Peptide Synthesis. Spring Venlag. N.Y. 1984.

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Preparation of compound A:

compound are pooled and lyophilized to dryness. The molecular weight of the reduced pressure to dryness. The dry resin is treated with TFA/TIS/water (92/5/3, v/v) a linear gradient of buffer A (1%TFA in Water/Nouffer B (1%TFA in CH<sub>3</sub>CN). The Trp(Boc)-Lys(Boc)-Abu-Cys(Acm)-Thr(tBu)-Rink amide MBHA resin (1 eq.), HBTU (2.9 eq), HOBt (3.0 eq.) and DIEA (6 eq) in DMF. The mbdure is shaken at room temperature for 4 hours. The resin is washed with DMF and DCM and dried under for 1 hour at room temperature. The solution is filtered and concentrated. To the concentrated solution is added cold ether. The precipitate is collected and dissolved in water-methanol solvent system. To the solution is added todine solution in methanol until the brown color appears. The solution then stands at room temperature for 1 hour To the solution is added Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous solution until the brown color disappears The resulting solution is purified by using a C18 reverse-phase prop HPLC, eluting with fractions are checked by analytical HPLC. The fractions containing pure desired Compound § (3 eq.) is mixed with H-(Doc)<sub>3</sub>-D-Phe-Cys(Acm)-Tyr(tBu)-D compound is measured by using MS fitted with an electrospray source. 2 2

Preparation of compound B:

Compound 12 where R1 is n-propyl (1.5 eq.) is mixed with H-D-Phe-Cys(Acm)-Tyr(Bu)-D-Trp(Boo)-Lys(Boo)-Lys(Boc)-Abu-Cys(Acm)-Thr(Bu) Rink amide MBHA resin (1 eq) and DIEA (2 eq) in DMF. The mixture is shaken at room temperature for 5 hours. The resin is washed with DMF and DCM and dried under reduced pressure to dyness. The dry resin is treated with TFA/TiS/water (92/5/3, v/v) for 1 hour at room temperature. The solution is fillered and concentrated. To the concentrated solution is added cold ether. The precipitate is collected and dissolved in water-methanol solvent system. To the solution is added lodine solution in methanol until the brown color appears. The solution then stands at room temperature for 1 hour. To the solution is added NeyS<sub>2</sub>O<sub>2</sub> aqueous solution until the brown color disappears. The resulting solution is purified by using a

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C18 reverse- phase prop HPLC, eluting with a linear gradient of buffer A (1%TFA in Waterybuffer B (1%TFA in CH<sub>2</sub>CN). The fractions are checked by analytical HPLC. The fractions containing pure destred compound are pooled and lyophilized to dryness. The molecular weight of the compound is measured by using MS fitted with an electrospray

Preparation of compound C:

resin (1 eq) and DIEA (2 eq) in DMF. The mixture is shaken at room temperature for 5 gradient of buffer A (1%TFA in Water)/buffer B (1%TFA in CH<sub>3</sub>CN). The fractions are hours. The resin is washed with DMF and DCM and dried under reduced pressure to temperature. The solution is filtered and concentrated. To the concentrated solution is system. To the solution is added todine solution in methanol until the brown color added Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous solution until the brown color disappears. The resulting Cys(Acm)-Tyr(tBu)-D-Trp(Boc)-Lys(Boc)-Abu-Cys(Acm)-Thr(tBu)-Rink amide MBHA dryness. The dry resin is treated with TFA/TIS/water (92/5/3, v/v) for 1 hour at room appears. The solution then stands at room temperature for 1 hour. To the solution is solution is purified by using a C18 reverse-phase prep HPLC, eluting with a linear checked by analytical HPLC. The fractions containing pure desired compound are pooled and lyophilized to dryness. The molecular weight of the compound is measured Compound 11 where R1 is n-propyl (1.5 eq.) is mixed with H-AEPA-D-Phe added cold ether. The precipitate is collected and dissolved in water-methanol solvern by using MS fitted with an electrospray source. 2 2 8

Preparation of compound D:

Compound <u>25</u> (3 eq.) is mixed with H-Doc-D-Phe-Cys(Acin)-Tyr(Bu)-D-Trp(Boc)-Lys(Boc)-Abu-Cys(Acin)-Thr(Bu)-Rink amide MBHA resin (1 eq.), HBTU (2.9 eq), HOBt (3.0 eq.) and DIEA (6 eq) in DMF. The mixture is shaken at room temperature for 4 hours. The resin is washed with DMF and DCM and dried under reduced pressure to dryness. The dry resin is breated with TFA/TIS/water (92/5/3, vv)

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purified by using a C18 reverse-phase prep HPLC, eluting with a linear gradient of  $Na_2S_2O_3$  aqueous solution until the brown color disappears. The resulting solution is cold ether, the precipitate is collected and dissolved in water-methanol solvent system. for 1 hour at room temperature. The solution is filtered and concentrated. To it is added buffer A (1%TFA in Water)/buffer B (1%TFA in CH<sub>8</sub>CN). The fractions are checked by To the solution is added iodine solution in methanol until the brown color appears. The lyophilized to dryness. The molecular weight of the compound is measured by using MS analytical HPLC. The fractions containing pure desired compound are pooled and solution is then stands at room temperature for 1 hour. To the solution is added

### fitted with an electrospray source.

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### Preparation of compound E:

MBHA resin (1 eq.), HBTU (2.9 eq), HOBt (3.0 eq.) and DIEA (6 eq) in DMF. The (1%TFA in CH3CN). The fractions are checked by analytical HPLC. The fractions collected and dissolved in water-methanol solvent system. To the solution is added DCM and dried under reduced pressure to dryness. The dry resin is treated with mixture is shaken at room temperature for 4 hours. The resin is washed with DMF and molecular weight of the compound is measured by using MS fitted with an electrospray containing pure desired compound are pooled and lyophilized to dryness. The phase prep HPLC, eluting with a linear gradient of buffer A (1%TFA in Water)/buffer B the brown color disappears. The resulting solution is purified by using a C18 reverseroom temperature for 1 hour. To the solution is added Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> aqueous solution until lodine solution in methanol until the brown color appears. The solution then stands at concentrated. To the concentrated solution is added cold either. The precipitate is TFA/TIS/water (92/5/3, v/v) for 1 hour at room temperature. The solution is filtered and Tyr(tBu)-Cys(Acm)-Tyr(tBu)-D-Trp(Boc)-Lys(Boc)-Val-Cys(Acm)-Trp(Boc)-Rink amide Compound 26 (3 eq.) is mixed with H-(D-Ser(Bu));-Lys(Boc)-D-Tyr(tBu)-D-

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### Preparation of compound E:

# Ethyl-[8-methyl-83-ergollnylmethy]]thioacetate

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methanesulforyl chloride. After stirring at room temperature for 2 hours, the reaction mixture was poured into 100 ml water, it was extracted with chloroform (2x 20 ml). To a solution of dihydrolysergol (240 mg) in 10 ml pyridine was added 250 µl

8 2 5 ಜ ĸ methanol and solvents were removed in Vacuo to give 40 mg of protected product Mass Spec. (Electrospray) 1500.7.

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in vacuo to dryness to give 140 mg of pale brown solid. Further extraction from Organic layer was washed with water, then dried over MgSO4 and solvent was removed Overall 240 mg. Mass Spec (Electrospray) 335.2. aqueous solution after basification with NaHCO3 gave another 100 mg of product

evaporation of solvent the residue was subject to preparative silica gel thin layer between chloroform and water. Organic layer was then dried (MgSQ<sub>4</sub>), and after ml dimethylformide was added powdered K<sub>2</sub>CO<sub>3</sub> (150 mg) followed by 150 µl ethyl-2: vacuo to dryness. Pale brown solid. 100 mg Mass spec (Electrospray) 359.2. chromatography using chloroform/methanol (9:1) as developing solvents. Appropriate mercaptoacetate and the mixture was heated at 40°C for 2 hours under nitrogen portion was isolated, extracted with chloroform-methanol and solvents were removed in atmosphere. Solvent was removed in vacuo to dryness, and the residue partitioned To a solution of the above D-6-methyl-8β-mesyloxymethyl-ergoline (140 ng) in 3

### Preparation of compound G:

# 6-Methyl-86-ergolinylmethylthioacetyl-D-Phe-c(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub> To a solution of 6-Methyl-8β-ergolimylmethylthioacetyl acid (Scheme I,

ethylcarbodiimlde-HCL), 100mg of HOAT (1-Hydroxy-7-azabezotrlazole) followed by (100 mg) prepared by solid-phase synthesis using Fmoc-chemistry in 10 ml compound 7) (50 mg) and D-Phe-c(Cys-Tyr(OBT)-D-Trp-Lys(BOC)-Abu-Cys)-Thr-NH<sub>2</sub> developing solvents. Appropriate portion was isolated, extracted with chloroformpreparative thin-layer chromatography using chloroform-methanol (85:15) as NaHCO3, dried over MgSO4. After evaporation of solvent, the residue was subject to between chloroform methanol and brine. The organic layer was washed with aqueous Volatile substances were removed in vacuo to dryness. The residue was partitioned dimethylformide was added 200 mg of EDC (1-[3-(dimethylamino)-propylj-3-200 µl dilsopropyletylamine and the mixture was stirred at room temperature overnight.

Volatile substances were removed in vacuo to dryness. The residue was purified using dichloromethal (10 ml) containing a few drops of tritsopropyl siliane for 30 minutes vydac C<sub>16</sub> HPLC and CH<sub>5</sub>CN/0.1% aqueous TFA, resulting in 17 mg of white solid Mass Spec (Electrospray). 1344.8, 673.2. The protected product was then treated with 30% trifluoroacetic acid in

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Preparation of compound H:

# Ethyl-(6-n-propyl-88-orgollnyl)methylthioacetate

This compound was prepared analogously to Compound F, starting with D-npropyt-88-hydroxymethylergoline which can be made according to EP 000.687. Pale

yellow solld. Mass Spec (Electropray) 387.2.

Preparation of compound I:

### 8-n-gropyl-88-ergolinylmethylthloacetyl-D-Phe-c(Cys-Tyr-D-Trp-Lys-Abu-Cys)-FAFE

рторун-8β-ergoliny)methytthloacetic acid (Scheme I, compound 6, where R1=propyl and 8=1) and D-Phe-c(Cys-Tyr(OBT)-D-Trp-Lys(BOC)-Abu-Cys)-Thr·NH2. White solid. This compound was prepared analogously to Compound G, starting with 6-n-Mass Spec. (Electrospray) 1372.5, 687.3. 으

Preparation of compound 1:

# 6-D-Mothyl-88-oracilin/Imethylthiaminosuccinoyl-D-Phe-c(Cvs-Tvr-D-Trp-Lvs-

Abu-Cys)-Thr-NH2

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This compound was prepared analogously to Compound G starting with 6-D-Methyl+8p-succinoylaminomethylergoline and D-Phe-c(Cys-Tyr(OBT)-D-Trp-Lys(BOC)-Abu-Cys)-Thr-NHz, White solid. Mass Spec (Electrospray) 1344.8, 673.2.

Preparation of compound K:

orgoline-D-Phe-c(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub>, i.e., a compound according 8-allyl-88-(1-ethyl-(3-N-methyl-3-carbonylmethyl)aminopropyl-ureidocarbonyl-ឧ

to the following structure:

1-fig-eil/Mergolin-8/g-yilcarbonyll-143-(N-fethoxycarbonyl)methyl.N-methyl) emine-propyll-3-ethylurea, i.e., a compound according to the following structure: ង

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3,3-BOC, N-Methylpropanedlamine

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mixture was stirred at room temperature overnight. After filtration, the filtrate was was added annhydrous MgSO4 (5.5gm) followed by benzaldehyde (2.3g) and the treated with (BOC); (4.3g) and DMAP (0.35g) and stirred for about 1 hour. The mixture was then washed with 5% aqueous citric acid, then 5% NaHCO3, and then dried over To a solution of 3 N-Methyl propanediamine (1.8g) in dichloromethane (30 ml)

After evaporation of solvent, the residue was dissolved in ethanol (50ml). Pd(OH), (600mg), acatic acid (1ml), and cyclohexene (3ml) were added and hydrogenation was carried out overnight. The mbture was fittered through a cellte pad and the filtrate was evaporated in vacuo to dryness to produce 3,3-BOC,N-Methylpropanediamine as a colonless liquid. 2.3 g. Mass Spec (Electrospray) = 189.1.

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6-allyl-86-(3,3-BOC,N-Methyl-aminopropyl-carbamoyl)-ergoline

To a solution of 6-ality-dihydrolyseralc acid (150mg), prepared according to the diethylcyanophosphonate (150µl) and the mixture was stirred at room temperature partitioned between CHCls and water. The organic layer was then washed with aqueous procedure disclosed in EP 0 003667, and 3,3-BOC,N-Methyl-propanediamine (150mg) in DMF (5ml) was added diisopropylethylamine (175µl) followed by overnight. Volatile substances were removed in vacuo to dryness. The residue was NaHCO, and dried over MgSO. Solvent was removed in vacuo to give 6-ally1-88-(3,3-2 ន

BOC,N-Methyl-aminopropyl-carbamoyl)-ergoline.

6-allyl-8p-(3-N-Methyl-aminopropyl-carbamoyl)-ergoline, TFA salt

6-allyl-8B-(3,3-BOC,N-Methyl-aminopropyl-carbamoyl)-ergoline

previous step was treated with 30% TFA in dichloromethane for 30 minutes and volatile substances were removed in vacuo to dryness yielding 250 mg of 6-allyf-8β-(3-N-Methyl-aminopropyl-carbamoyl)-ergoline, TFA salt. Mass spec (Electrospray) = 367.2. ม

6-allyt-8g-(3-N-Methyl,3-carbethoxymethyl)aminopropyl-carbamoyl-ergoline

To a solution of 6-allyl-8p-(3-N-Methyl-aminopropyl-carbamoyl)-ergoline TFA the residue was partitioned between chloroform and water. The organic layer was dried Methyl,3-carbethoxymethyl)aminopropyl-carbamoyl-ergoline (240mg). Mass Spec salt (250mg) and K<sub>2</sub>CO<sub>3</sub> (140mg) in DMF (5ml) was added ethyl bromoscetate (70µJ) and the mixture was stirred at room temperature overnight. After evaporation of solvent, using MgSO, and then solvent was removed in vacuo to give crude 6-allyl-86-(3-N-(Electrospray) = 453.2. 8

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6-altyl-8β-(1-ethyl-(3-N-methyl-3-carbethoxymethyl)aminopropyl-ureidocarbonyl-

carbethoxymethy:)aminopropyi-uraidocarbonyi-ergoline as a pale yellow viscous chromatography using chloroform/methanol (19 to 1) as developing solvents. added. The mixture was refluxed under nitrogen etmosphere for 3 days and after the previous step was dissolved in toluene (10ml) and ethylisocyanate (3ml) was substance (30mg). Mass Spec (Electrospray) = 524.3. Appropriate portion was extracted with chloroform/methanol and solvents were evaporation of volatile substances, the residue was subject to preparative silica get 6-allyl-8β-(3-N-Methyl,3-carbethoxymethyl)aminopropyl-carbamoyl-ergoline from vacuo ਰ evig evig 6-allyl-8β-(1-ethyl-(3-N-methyl-3-

6-allyl-8ß-(1-ethyl-(3-N-methyl-3-carboxymethyl)aminopropyl-ureidocarbonylergoline, i.e., a compound according to the following structure:

8 ಭ organic extract is dried and the solvents are removed in vacuo to yield 6-allyi-86-(1ethyl-(3-N-methyl-3-carboxymethyl)aminopropyl-ureidocarbonyl-ergoline. mixture is addified with 5% aqueous citric acid and extracted with CHCl3-Methanol. The MA). The mixture is incubated on a rotary shaker at approximately 40 C overnight. The phosphate buffer (pH=approx. 7) and 0.6ml ChlroCLEC-BL (Altus Biologics, Cambridge, ureldocarbonyl-ergoline (520 mg) in 10 ml of acetone are added 15 ml of 0.2M To a mixture of 6-allyl-8β-(1-ethyl-(3-N-methyl-3-carbethoxymethyl)aminopropyl-

6-ellyl-86-(1-ethyl-(3-N-methyl-3-carbonylmethyl)aminopropyl-ureidocarbonylergoline-D-Phe-c(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub>, I.e., Compound K

ureidocarbonyl-ergoline (50 mg) and D-Phe-c(Cys-Tyr-D-Trp-Lys(FMOC)-Abu-Cys)vacuo to dryness. The residue is partitioned between chloroform methanol and brine of HOAT (1-Hydroxy-7-ezabezotriazole) followed by 200 µl disopropyletylamine and the added 200 mg of EDC (1-{3-(dimethylamino)-propyl}-3-ethylcarbodiimide-HCL), 100mg evaporation of solvent the protected product is then treated with 5% piperidine in DMF The organic layer is washed with aqueous NaHCO<sub>3</sub> and then dried over MgSO<sub>4</sub>. After mixture is stirred at room temperature overnight. Volatile substances are removed in Thr-NH<sub>2</sub> (100 mg, prepared by solid-phase synthesis), in 10 ml dimethylformide is To a solution of 6-allyl-80-(1-ethyl-(3-N-methyl-3-carboxymethyl)aminopropyl-

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8 5 Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin 0.45M

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yield the purified, de-protected product. about 2 ml). It is purified using VYDAC C18 HPLC and CH3CN/0.1% aqueous TFA to (10 ml) for 30 minutes. Volatile substances are removed in vacuo to a small volume (

Example

A. H-Aepa-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-

ઇ DTyr(tBu)-OH Fmoc-Phe-OH, Fmoc-Cys(Trl)-OH, Fmoc-Thr(tBu)-OH and Fmoc-Abuprotecting group with 20% piperidine in NMP for 30 min, (3) washing with NMP, (4) Cys(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-DTrp(Boc)-OH, Fmoc-Tyr(tBu)-OH, Fmoo (Foster City, CA) model 433A peptide synthesizer by using Fluorenylmethyloxycarbonyl successively according to the sequence. After peptide chain was assembled, the Fmoc to perform the following reaction cycle: (1) washing with NMP, (2) removing Frace of NMP were added to the resin. The ABI 433A peptide synthesizer was programmed (DMF). This activated amino acid ester, 1mL of diisopropylethylamine (DIEA) and 1mL CA) were used with the following side chain protection: Fmoc-Thr(tBu)-OH, Fmoc substitution of 0.72 mmol/g was used. The Fmoc amino acids (AnaSpec, San Jose was removed and washed completely by using DMF and dichloromethane (DCM). coupling with pre-activated Fmoc amino acid for 1h. hexafluorophosphate/1-hydroxy-benzotriazole (HBTU/HOBT) in N,N-dirrethyfformamide each coupling step, the Fmoc amino acid (4 eq, 1 mmol) was first pre-activated in 2ml removed by treatment with 20% piperidine in N-methylpyrrolidone (NMP) for 30 min. In IL). The synthesis was carried out on a 0.25 mmol scale. The Fmoc groups were OH. Fmoc-Aepa-OH was purchased from Chem-Impex International, Inc. (Wood Dale, (Fmoc) chemistry. A Rink Amide MBHA resin (Novabiochem., San Diego, CA) with The protected peptide-resin was automatically synthesized on an Applied Biosystems 2-(1-H-benzotriazole-1-yl)-1,1,2,3-tetramethyluronium The resin was coupled

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MBHA= 4-methylbenzylhydrylamine

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yłoxytris(pyrrolidino)phosphonium-hexafluorophosphata] ( PyAOP ) (148 mg. 028 treated with a mixture of TFA, H<sub>2</sub>O and trilsopropy/silane (TIS) (9.5 ml / 0.85ml /0.8 ml) 100ml of 5% AcOH aqueous solution, to which lodine methanol solution was added 1h. 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> water solution was added to quench excess lodine. The crude product C18 DYNAMAX-100 A°(Varlan, Walnut Creek, CA). The column was eluted with a 0.1% TFA in water and B was 0.1% TFA in acetonitrile. The fractions were checked by with compound Z (92 mg, 0.28 mmol, 1.5 eq.), ), [7-azabenzotrlazol-1mmol, 1.5 eq.) and 1-hydroxy-7-azabenzotrlazol (HOAT) (38 mg, 0.28 mmol, 1.5eq.) In successively with DMF, methanol and DCM. After drying in the air, the resin was for 2h. The resin was filtered off and the filtrate was pouned into 50 mL of cold ether. The precipitate was collected after centrifuge. The crude product was dissolved in dropwise until yellow color maintained. The reaction solution was stimed for additional in the solution was purified on preparative HPLC system with a column (4x43cm) of linear gradient from 80% A and 20% B to 55%A and 45% B in 50 min., where A was an analytical HPLC. Those containing pure product were pooled and lyophilized to dryness. Yield: 40%. The purity was 96.8% based on analytical HPLC analysis. MS Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin (0.188 mmol) was mixed 5 mL of DCM. The mbdure was shaken overnight. The resin was drained and washed В. The resulting H-Aepe-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTrp(Boc) (Electro Spray): 1820.8 (in agreement with the calculated molecular weight of 1821.3). 2 으 8

25 Example M

Example M was synthesized substantially according to the procedure described for Example L by using H-Lys(Boc)-DTyr(tBu)-DTyr(tBu)-Cys(Trt)-Tyr(tBu)-DTp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin, Purity of the final product

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was 97.9% based on analytical HPLC analysis. MS (Electro Spray); 1652.1 (in agreement with the calculated molecular weight of 1652.03).

Example N

Example N was synthesized substantially according to the procedure described for Example\_L by using H-Doc-Lys(Boc)-DTyr(Bu)-DTyr(Bu)-Cys(Trt)-Tyr(Bu)-DTyr(B

Fmoc-Doc-OH was purchased from Chem-Impex International, Inc. (Wood Dale, IL).

Cample C

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Example O was synthesized substantially according to the procedure described for EXAMDIE\_L by using (6-N-propyl-8β-ergolinyl)methylthioacetic acid and H-Lys(Boc)-20 DTyr(Bu)-DTyr(Bu)-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-RInk Amide MBHA Resin. Purity of the final product was 97.4% based on analytical HPLC analysis. MS (Electro Spray): 1680.8 (in agreement with the calculated molecular weight of 1680.1).

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#### Example P

Example P was synthesized substantially according to the procedure described for <a href="Example\_L">Example\_L</a> by using (6-N-propyl-8β-orgolinyl)methylithicacetic acid and H-Aepa-Aepa-D-Pho-Cys(Trt)-Tlyr(iBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(iBu)-Rink Amide MBHA Resin. Purity of the final product was 99.9% based on analytical HPLC analysis. MS (Electro Spray): 1710.7 (in agreement with the calculated molecular weight of 1711.2).

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Example Q was synthesized substantially according to the procedure described for Example L by using (6-N-propyt-8p-ergolinyl)methythicacetic acid and H-Aepa-Aepa-DPho-Cys(Trt)-(3-lodo)Tyn-DTrp(Boc)-Lys(Boc)-Val-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin. Purity of the final product was 99% based on analytical HPLC analysis. MS (Electro Spray): 1851.1 (in agreement with the calculated molecular weight of 1851.1).

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Fmoc-(3-lodo)-Tyr-OH was purchased from Advanced ChemTech (Louisville, KY).

3-lodo)Tyr=

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#### Example B

Example R was synthesized substantially according to the procedure described for <a href="Example">Example</a>, by using H-Aepa-DPhe-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-5 Thr(tBu)-Rink Amide MBHA Resin. Purity of the final product was 98.3% based on analytical HPLC analysis. MS (Electro Spray): 1513.8 (in agreement with the calculated

#### Example S

molecular weight of 1513.9).

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Example S was synthesized substantially according to the procedure described for <a href="Example">Example</a> by using H-Aepa-Aepa-DPho-Cys(Trt)-(3-lodo)Tyr-DTrp(Boc)-Lys(Boc)-Vel-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin. Purity of the final product was 85.7% based on analytical HPLC analysis. MS (Electro Spray): 1822.9 (In agreement with the calculated molecular weight of 1823.06).

#### Example T

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Example T was synthesized substantially according to the procedure described for <a href="Example">Example</a> L by using H-Doc-DPhe-Cys(Trt)-Tyr(tBu)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(tBu)-Rink Amide MBHA Resin. Purity of the final product was 98.9% based on analytical HPLC analysis. MS (Electro Spray): 1489.6 (in agreement with the calculated molecular weight of 1489.84).

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Example U was synthosized substantially according to the procedure described for <u>Example L</u>, by using H-Doc-DPhe-Cys(Trt)-(3-lodo)Tyr-DTm(Boc)-Lys(Boc)-Vals Cys(Trt)-Thr(Bu)-Rink Amide MBHA Resin. MS (Electro Spray): 1629.8 (in agreement with the calculated molecular weight of 1629.7).

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10 The titled compound was synthesized substantially according to the procedure described for Example L by using H-Doc-Doc-Dorho-Cys(Trt)-Tyr(t8u)-DTrp(Boc)-Lys(Boc)-Abu-Cys(Trt)-Thr(t8u)-Rink Amide MBHA Resin. Purity of the final product was 99% based on analytical HPLC analysis. MS (Electro Spray): 1635.0 (in agreement with the calculated molecular weight of 1633).

Some of the compounds of the instant invention can have at least one asymmetric center. Additional asymmetric centers may be present on the molecule depending upon the nature of the various substituents on the molecule. Each such asymmetric center will produce two optical isomers and it is intended that all such optical isomers, as separated, pure or partially purified optical isomers, racemic mixtures or diasternomenic mixtures thereof, are included within the scope of the instant invention.

The compounds of the instant invention generally can be isolated in the form of their pharmaceutically acceptable acid addition salts, such as the salts derived from using inorganic and organic acids. Examples of such acids are hydrochloric, nitric, sulfurke, phosphoric, formic, acetic, trifluoroacetic, propionic, maleic, succinic, D-tartaric, L-tartaric, maionic, methane sulfonic and the like. In addition, certain compounds containing an acidic function such as a carboxy can be isolated in the form of their

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Inorganic sait in which the counter-ion can be selected from sodium, potassium, lithium, calcium, magnesium and the like, as well as from organic bases.

The pharmacautically acceptable salts can be formed by taking about 1 equivalent of a compound of the invention, (e.g., Compound C, below), and contacting it s with about 1 equivalent or more of the appropriate corresponding acid of the salt which is desired. Work-up and isolation of the resulting salt is well-known to those of ordinary skill in the art.

The compounds of this invention can be administered by oral, parenteral (e.g., intramuscular, intraperfloneal, intravenous or subcutaneous injection, or implant), nasal, so vaginal, rectal, sublingual or topical routes of administration and can be formulated with pharmaceutically acceptable carriers to provide dosage forms appropriate for each route of administration. Accordingly, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingradient, at least one compound of the invention in association with a pharmaceutically acceptable carrier.

Solid dosage forms for oral administration include capsules, tablets, pills, powders and granules. In such solid dosage forms, the active compound is admixed with at least one inert pharmaceutically acceptable carrier such as sucrose, lactose, or starch. Such dosage forms can also comprise, as is normal practice, additional substances other than such inert diluents, e.g., lubricating agains such as magnesium stearate. In the case of capsules, tablets and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coadings.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, the elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvents, such as wetting agents, emulsifying and suspending agents, and sweetening, flavoring and perfuming agents.

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Preparations according to this invention for perentaral administration include starile aqueous or non-aqueous solutions, suspensions, or emulsions. Examples of non-aqueous solvents or vehicles are propylene glycol, polyethylene glycol, vegetable oils, such as olive oil and com oil, gelatin, and injectable organic esters such as ethyloleate. Such dosage forms may also contain adjuvants such as preserving, wetting, emulsifyling, and dispersing agents. They may be sterilized by, for example, filtration through a bacteria-retaining filter, by incorporating starilizing agents into the compositions, or by healting the compositions. They can also be manufactured in the form of sterile solid compositions which can be

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dissolved in sterile water, or some other sterile injectable medium immediately before use.

Compositions for rectal or vaginal administration are preferably suppositories which may contain, in addition to the active substance, excipients such as coca butter

Compositions for nasal or sublingual administration are also prepared with standard excipients well known in the art.

in general, an effective dosage of active ingredient in the compositions of this invention may be varied; however, it is necessary that the amount of the active ingredient be such that a sullable dosage form is obtained. The selected dosage depends upon the desired therapeutic effect, on the route of administration, and on the duration of the treatment, all of which are within the realm of knowledge of one of ordinary skill in the art. Generally, dosage levels of between 0.0001 to 100 mg/kg of body welght daily are administered to humans and other animals, e.g., mammals.

15 A preferred dosage range is 0.01 to 10.0 mg/kg of body weight daily, which can be administered as a single dose or divided into multiple doses. Somatostatin Receptor Specificity and Selectivity Assay

Specificity and selectivity of the somatostatin analogues used to synthesize the somatostatin-dopamine chimers were determined by a radioligand binding assay on CHO-K1 cells stably transfected with each of the SSTR subtypes, as follows.

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The complete coding sequences of genomic fragments of the SSTR 1, 2, 3, and 4 genes and a cDNA clone for SSTR 5 were subcloned into the mammalian expression vector pCMV (Life Technologies, Milano, Italy). Clonal cell lines stably expressing SSTR's 1-5 were obtained by transfection into CHO-K1 cells (ATCC, Manassas, Va, USA) using the calcium phosphate co-precipitation method (Davis L, et al., 1994 In: Basic methods in Molecular Biology, 2nd edition, Appleton & Lange, Norwelk, CT, USA:

611-646). The plasmid pRSV-neo (ATCC) was included as a selectable marker.

Clonal cell lines were selected in RPMI 1640 media containing 0.5 mg/ml of G418 (Life

Technologies, Milano, Italy), ring cloned, and expanded into culture.

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Membranes for in vitro receptor binding assays were obtained by homogenizing the CHO-K1 cells expressing the SSTR's subtypes in ice-cold 50 mM Tris-HCl and centrifuging twice at 39000 g (10 min), with an intermediate resuspension in fresh buffer. The final pellets were resuspended in 10 mM Tris-HCl for assay. For the SSTR 1, 3, 4, and 5 assays, aliquots of the membrane preparations were incubated 90 min. at 25°C with 0.05 nM [<sup>12k</sup>-Tyr11]SS-14 in 50 mM HEPES (pH 7.4) containing 10 mg/ml BSA, 5 mM MgCb, 200 KIU/mì Trasylol, 0.02 mg/ml bactracin, and 0.02 mg/ml

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phenyimethylsuphonyl fluoride. The final assay volume was 0.3 ml. For the SSTR 2 assay, 0.05 nM [\*2]MK-878 was employed as the radioligand and the incubation time was 90 mln at 25 °C. The incubations were terminated by rapid filtration through GF/C filters (pre-soaked in 0.3% polyethylenimine) using a Brandel filtration manifold. Each tube and filter were then washed three times with 5 ml alliquots of loo-cold buffer. Specific binding was defined as the total radioligand bound minus that bound in the presence of 1000 nM SS-14 for SSTR 1, 3, 4, and 5, or 1000 nM MK-678 for

Dopamine Receptor Specificity and Selectivity Assay

O Specificity and selectivity for the dopamine-2 receptor of the dopamine analogues used to synthesize the somatostatin-dopamine chimers may be determined by a radioligand binding assay as follows.

Crude membranes were prepared by homogenization of frozen rat corpus striatum (Zivic Laboratories, Pittsburgh, PA) in 20 ml of ico-cold 50 mM Tris-HCl with a Brinkman Polytron (setting 6, 15 sec). Buffer was added to obtain a final volume of 40 ml, and the homogenete was centrifuged in a Sorval SS-34 rotor at 39,000 g for 10 min at 0-4 °C. The resulting supernatant was decented and discarded. The pellet was rehomogenized in ico-cold buffer, pre-incubated at 37 °C for 10 min, diluted, and centrifuged as before. The final pellet was resuspended in buffer and held on ice for

For assey, allquots of the washed membrane preparations and test compounds were incubated for 15 min (37 C) with 0.25 nM (3H)|spiperone (16.5 Ci.mmol, New England Nuclear, Boston, MA) in 50 mM Tris HCi, 120 mM NaCi, 5 mM KCi, 2 mM CaCi2, 1 mM MgCi2. The final assay volume was 1.0 ml. The incubations were terminated by rapid filtration through GF/B filters using a Brandel filtration manifold. Each tube and filter were then washed three times with 5-ml aliquots of ice-cold buffer. Specific binding was defined as the total radioligand bound minus that bound in the presence of 1000 nM (+) butaclamol.

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the receptor binding assay.

### Other Embodiments

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It is to be understood that while the invention has been described in conjunction with the detailed description thereof, that the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the claims. Also, all publications mentioned herein are hereby incorporated by reference in their entirety.

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Claims

A compound of the formula (i),

What is claimed is:

X Is H, CI, Br, I, F, -CN, , or C, a alkyl;

R1 is H, C14 alkyl, alkyl, alkenyl or -CN;

R2 and R3, each are, independently H or absent, provided that when R2 and R3 are absent a double bond is present between the carbon atoms to which they are attached; 2

R4 is H or -CH3;

YB-O., -C(0)., -S., S-(CH2)S-C(0)., -S(0)., -S(0)., -SC(0)., -OC(0).

R5, R6, R7 and R8 each is, independently, H or C<sub>14</sub> alkyl; or -N(R6)-;

R8 is H or C1.8 alkyl;

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m ls 0 or 1;

n Is 0-10;

L is -{CH<sub>2</sub>}p-C(O)-, when Y is -S-, -S(O)-, -S(O)<sub>2</sub>-, -O- or -N(R6)-;

L Is -C(O)-(CR7R8)q-C(O), when Y is -N(R6)-, -O., or -S-;

L is (Doc)t-, when Y is -C(O)-, SC(O)-, -OC(O)-, -S-(CH2)s-C(O)-, or -N(R5)-C(O)-;

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p is 1-10;

q is 2-4;

s is 1-10;

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Z is somatostatin analog or a molety comprising -H, -OH,  $(C_1 - C_6)$ alkoxy, arylalkoxy, -NH2, or -NR9R10, wherein R9 and R10 each is, independently, H or C14 alkyl; t is 1-10; and

or a pharmaceutically acceptable salt thereof.

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X Is H, CI, Br, I, F, -CN, , or C, alkyl:

R1 is C1-4 alkyl, H, allyl, alkenyl or -CN;

R2 and R3, each are, Independently H or absent, provided that when R2 and R3 are absent a double bond is present between the carbon atoms to which they are attached;

R5 is C1-5 alkyl group, or a group of the formula of -(CH2)rN(CH3)q; R4 is H or -CH3; 2

Y is -O., -C(O)-, .S., -SC(O)-, -OC(O)-, -N(RB)-C(O)-, -N(R7)-, or -N(RB)-(CH\_)S-C(O)-;

R6, R7, R8, R9 and R10 each is, independently, H or C1-s alkyl;

L is -C(O)-(CR9R10)q-C(O)-, when Y is -N(R7)-, -O-, or -S-; L is -(CH<sub>2</sub>)p-C(O)-, when Y is -S-, -O- or -N(R7)-;

L is -{Doc)t-, when Y is -C(O)-, SC(O)-, -OC(O)-, -N(RB)-(CH2)s-C(O)-, or -N(RB)-C(O)-2

m ls 0 or 1;

n is 2-10;

rls 1-8,;

q is 2-4;

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p is 1-10;

s ts 1-10;

t is 1-10; and

Z is somatostatin analog or a molety comprising -H, -OH, (C,-C<sub>4</sub>)alkoxy, arylalkoxy, .

NH2, or -NR9R10; ห

or a pharmaceutically acceptable salt thereof.

3. A compound of the formula:

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D-Nat-cyclo[Cys-Tyr-D-Trp-Lys-Vat-Cys]-Thr-NH<sub>2</sub>

/ D-Phe-cyclo[Cya-Tyr-D-Trp-Lya-Thr-Cys]-Nal-NH<sub>2</sub>

D-Phe-cyclo(Cys-(3-Bromo-Tyr)-D-Trp-Lys-Thr-Cys)-Thr-NH<sub>2</sub>

/(Doc)<sub>2</sub>-D-Phe-cyclo(Cys-Tyn-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub>

-s/| (Doch-D-Phe-ordo)(Oye-Tyr-D-Tip-Lys-Abu-Oye)-Tir-NH-

Doc-Nb-D-Tyr-D-Sar-cyclo[Cys-Pha-D-Trp-Lys-Thr-Cys}-Thr-NH<sub>2</sub> /(Doc)<sub>z</sub>-Lys-D-Tyr-D-Tyr-cyclo(Cys-Phs-D-Typ-Lys-Thr-Cys)-Thr-NH<sub>2</sub>

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(DSer), Nie-D-Tyr-D-Ser-cyclo(Cys-Phs-D-Trp-Lys-Thr-Ojs)-Thr-NH<sub>2</sub> (Doc)<sub>3</sub>-Lya-D-Tyr-D-Tyr-cyclo(Cya-Pha-D-Trp-Lya-Thr-Cya)-Thr-NH<sub>2</sub>

\_\_\_\_\_\_\_(D-Ser),<sub>0</sub>-Lys-D-Tyr-D-Tyr-oyclo(Cys-Pho-D-Trp-Lys-Thr-Oys)-Thr-NH<sub>y</sub>

H Sen'y-Lys-D-Tyr-D-Tyr-opto(Oys-Pho-D-Trp-Lys-Thr-Oys)-Thi-ANH<sub>y</sub> D-Phe-cyclo(Cys-Phe-D-Trp-Lys-Thr-Cys)-Thr-oi

'S (Doc)<sub>3</sub>-D-Phe-cyclo[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr-of

- D-Phe-cyclo(Cys-Tyr-D-Trp-Lys-Val-Cys)-Trp-NH<sub>2</sub>

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H (Doc), D-Pha-cyclo(Co-Ty-D-Trp-Lya-Val-Cya)-Trp-NH,

Caeg = N-(2-eminoethyl)-N-(2-cytosinyl-1-oxo-ethyl)-glycine

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HI S Optidion-Pre-Typo-Trp-Lye-Tre-Pre-Opj-NH-, H NO DOOL-Openio Pro-Dirp-tys-Tra-Pro-Cys-NN-, S CODOCOM-Pre-Pre-D-Trp-1/s-Tra-Pre-Cys]-NH-, Doo-cyclo(Cys-Phe-Php-D-Trp-Lys-Thr-Phe-Cys-J-NH<sub>2</sub> -Doo-cyclo(Cya-Pha-Tyr-D-Trp-Lya-Thr-Pha-Cya)-NH<sub>2</sub>

HN S (Dool), Lise D. Tyr Orde(O)se Phase Phase Tro Lise The Phase O)sel Nis.

DPhieopdqOpe-Tyr-O-Trp-Lye-Thr-OpenhashNit-L-D-Pha-cyclo(Cya-(3-Bromo-Tyr)-O-Trp-Lya-Thr-Cyaj-Thr-NH<sub>2</sub>

HAN D Nai-cycla(Cys-Tyr-D-Trp-Lys-Vai-Oys)-Trr-NN's

Ser-cyclo(Cys-Phe-Phe-D-Trp-Lys-Thr-Phe-Cys]-NH<sub>2</sub>

HN S (Doo), Lys-D-Tyr-D-Tyr-D-Try-Pne-Oys)-NH,

HN S (Dock-cyclo(Cys-Phe-Tyr-D-Trp-Lys-Thr-Phe-Cys)-NH<sub>2</sub>

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-D-Phe-cyclo(Cye-Tyr-O-Trp-Lye-Abu-Cye)-Thr-NHy, Compound B

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——(D-Set)<sub>10</sub>-Lys-D-Tyr-Oydd(Cys-Phs-O-Trp-Lys-Thr-Cys)-Thr-Ath<sub>1</sub>

.... (D-Sor),-Lys-D-Tyr-cyclq(C)s-Pha-D-Trp-Lys-Tra-Cys)-Thr-NH,

Defrespendicye-Tyr-D-Trp-Lye-Trp-Cyg-Nete-NH4,

Dockston Tyrocking Pre-Pre-D Trps: pr-Trps: Pre-Pre-D Trps: pr-Trps: Pre-Pre-D Trps: pr-Trps: pr-Trps:

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H H (Dock, O-Pinespeal Ope Tyr D-Try-Lye-Abu-Cys)-Tra-NH1,

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D. Sert, Alex D-Ty-D-Ser optid Die-Phe-D-Tip-Lye-The-Oys)-The-NH-i, HN (Doc)<sub>2</sub>O-Phe-cycle(Ope-Tyr-O-Tip-Lye-Abur-Ope)-Thr-Net-L H (Dook-Lya-D-Tyr-O)dd(O)a-Fila-D-Tip-Lya-Tirr-Oya)-Tirr-dis-H (Dock-Lyn-D-Tyn-D-Tyn-Opde)Cyn-Phin-D-Trp-Lyn-Thr-Cyntj-Thr-KNt, DSark-Lya-D-Tyn-Opdo(Oya-Pha-D-Tyn-Lya-Thr-Oya)-Thr-Vis--D-Pha-cycld(Cya-Pha-D-Trp-Lya-Thr-Cya)-Thr-ol

D.Pheopda(Ope-Tyr-O-Trp-Lye-Val-Oye)-Trp-NH-1, H (Doc), D Pheopadice Tyr O Tip Lyr Viz Oys) Tip HH, H Doc-Ne-D-Tyr-D-Ser-opdi(Op-Tyr-D-Trp-Lye-Val-Opp)-Trp-Nti, H (Dock-tyn-O-Tyn-O-Tyn-OpdelOye-Tyn-O-Trp-tyn-Van-Oyel-Trp-klis, H Doxy-tys-D7y-O7y-OctdOs-Ty-D-Toxtys-Vas-Op)-ToxHil-

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D.Sarj, Nie-D-Tyr-D-Sar-oydd(Cye-Tyr-D-Typ-Lye-Vie-Oys)-Tip-Nii-

Dock D-Phaopid(Os-Pha-D-Tip-Lys-Thr-Ose)-Thr-d Dookto-D-Ty-D-Ser-cycla(Ope-Tyr-D-Trp-Lye-Val-Ope)-Trp-NH<sub>2</sub> D-Phacyclo(Cya-Tyr-D-Trp-Lya-Val-Cya)-Trp-NH<sub>2</sub> D-Pha-cyclo(Cys-Pha-D-Trp-Lys-Thr-Cys)-Thr-of (Doc),-D-Phe-cyclo(Dys-Tyr-D-Trp-Lys-Va:-Oys)-Trp-NH, ─ (Doc)¿Lya-O-Tyn-O-Tyn-Oydo(Cya-Tyn-O-Tp-Lya-Val-Cya)-Trp-NH, — (Dac)<sub>2</sub>-Lya-D-Tyr-D-Tyr-cydd(Cyn-Tyr-D-Trp-Lya-Val-Cya)-Trp-NH<sub>2</sub>

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H (CH,), O (Dec), D Phe cycl(Op Tyr D Trp Lys Abu-Ops) Thr Alliq

HAVE OF IDOCK-O-Pile optid Ope Tyr-D-Trp-Lys-Abu-Ope|-Thr-ANH,

H (CH,); O DOD NO - D TYP D Servopad (One Promp D Trip Lyo - The Opi + The ANH, a

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HAT O HAT O O OTHER ORDINA DE TYPO DE Doc-Nie-D-Tyr-D-Ser-cydd(Cys-Tyr-D-Trp-Lys-Val-Cys)-Trp-NH<sub>2</sub> (Doc)<sub>3</sub>-Lys-D-Tyr-D-Tyr-Oyclo(Oys-Tyr-D-Trp-Lys-Val-Oys)-Trp-NH<sub>2</sub> HN CH, CH, The Cyclo(Cys-Tyr-D-Trp-Lys-Va;-Cys)-Trp-NH-2 HN ONH O (DSer/k-Lys-D-Tyr-D-Tyr-cyclo(Oys-Tyr-D-Tip-Lys-Val-Oys)-Tip-NH-(CH) H (CH) H (D-Ser) RNIe-D-Tyr-D-Ser-opto(Cyr-Tyr-D-Trp-Lyr-Val-Oys)-Trp-NH<sub>2</sub> D-Pho-cydo(Cys-Tyr-D-Trp-Lys-Val-Cys)-Trp-NH<sub>2</sub> 

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H (CH.IJ-O (DSenjalle-DT)#-DSencyad(Cye-Tyr-D-Trp-Lye-Vet-Cye)Trp-Nis,

H CH4) CH4) C COSM, Lys D.Tys OpidCos Tys D.To Lys Via Cost To Lys Via Cost To

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--- Doc-D-Phe-cyclo(Cye-Phe-D-Trp-Lye-Thr-Cys)-Thr-di

Lys-D-Tyr-D-Tyr-oydd(Op-Pho-D-Trp-Lys-Thr-Oys)-Thr-d L-Doo-Nie-D-Tyr-D-Ser-cyclo(Cys-Pho-D-Trp-Lys-Thr-Cys)-Thr-di L\_(D-Ser)<sub>to</sub>-Lya-D-Tyr-D-Tyr-cyclq(Oya-Pha-D-Typ-Lya-Thr-Cya)-Thr-d —(Dac)<sub>e</sub>-D-Pho-cycla(C)s-Pho-D-Trp-Lys-Thr-Ojs}-Thr-di — AEPA-D-Pho-cycld(Cyo-Pho-D-Try-Lyo-Thr-Cyo)-Thr-cl

Doo-Nis-D-Tys-D-Ser-cycld(Cys-Pha-D-Trp-Lys-Thr-Cys)-Thr-d Lya-D-Tyr-D-Tyr-cyclogo-Pha-O-Trp-Lya-Thr-Oxal-Thr-of Dock-O-the-cyclope-Phe-O-Trp-Lys-Thr-O/a)-Thr-ol L—(Dcc),-O-Pha-cyclo(Cys-Pha-D-Trp-Lys-Thr-Cys)-Thr-ol L\_ (D-Sar)<sub>W</sub>-Lye-D-Tyr-D-Tyr-cycld(Cye-Phe-D-Typ-Lye-Thr-Cye)-Thr-d L-(D-Ser),-Lya-D-Tyr-D-Tyr-cyclo[Cya-Pha-D-Trp-Lya-Thr-Cya-FThr-ol — AEPA-D-Pho-cyclo(Cyo-Pho-D-Trp-Lys-Thr-Cys}-Thr-ci

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-DooD-Phe-cyclo(Cys-Phe-D-Trp-Lys-Thr-Cys)-Thr-d

O (DOC), OP PRECYCLOS PRED TREVET PROSPING

- Doc-Nie-D-Tyr-D-Sencyclo(Cye-Phe-D-Trp-Lys-Thr-Cys)-Thr-d

- (Doc), -D-Phe-cyclo[Cye-Phe-D-Trp-Lye-Thr-Cys]-Thr-ol

- DSeyLya-DTy-O-Tyr-OydqOya-Pha-D-Trp-Lya-Thr-Cyal-Thr-d

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S Doc-Lya-DTyr-D-Tyr-cydd(Cya-Pha-D-Trp-Lya-Val-Cya)-Thr-NH-,

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or a pharmaceutically acceptable salt thereof. ধু.স. তেলাpound according to the comuna.

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/(Doc)<sub>Z</sub>-Aepe-Lys-DTyr-D-Tyr-cydo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Trr-NH<sub>Z</sub>

(Doc)<sub>b</sub>-Aepe-Lys-DTyr-D-Tyr-cydo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub>

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(Doc)<sub>2</sub>-(Aspa)<sub>2</sub>-Lys-DTyr-D-Tyr-cydo[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>2</sub>

(Aepa)<sub>z</sub>-D-Phe-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub>

/(Doc)<sub>6</sub>-Aepa-Lya-DTyr-D-Tyr-cydo[Cya-Tyr-D-Trp-Lya-Abu-Cys]-Thr-NH<sub>2</sub>

'(Doc)<sub>4</sub>-Aepa-Lys-DTyr-D-Tyr-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys|-Thr-NH<sub>2</sub>

(Doc)<sub>6</sub>-Aspa-Lys-DTyr-D-Tyr-cydo|Cys-Tyr-D-Trp-Lys-Abu-Cys}-Thr-NH<sub>2</sub>

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Lys-DTyr-D-Tyr-cydo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub>

/Aspa-Lya-DTyr-D-Tyr-cydo(Cya-Tyr-D-Trp-Lya-Abu-Cys)-Thr-NH<sub>2</sub>

Doo-Aepa-Lya-DTyr-D-Tyr-cyclo(Cya-Tyr-D-Typ-Lya-Abu-Cya)-Thr-NH<sub>2</sub>

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/(Doc),-D-Phe-cyclo(Cya-(3-lodo-Tyr)-D-Trp-Lya-Val-Cys)-Thr-NH<sub>2</sub>

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Aspa-D-Pha-cydo(Cya-(3-lodo-Tyr)-D-Trp-Lya-Val-Cys)-Trr-NH<sub>2</sub>

(Doc); Aepa-Lya-DTyr-D-Tyr-cyclo(Cya-Tyr-D-Trp-Lya-Abu-Cya)-Thr-Nife (Doc);-Aepa-Lys-DTyr-D-Tyr-cydo(Cys-Tyr-D-Trp-Lys-Abu-Cys}-Thr-NH 2 Lys-DTyr-D-Tyr-cydo[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH 2 (Dock-Aepa-Lya-DTyr-D-Tyr-cydd(Cya-Tyr-D-Trp-Lya-Abu-Cys)-Thr-NH 2 (Dock-Aepa-Lys-DTyr-D-Tyr-cydo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH /(Dock-Aepa-Lys-DTyr-D-Tyr-cydo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH /Aepa-Lys-DTyr-D-Tyr-cydo[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH /(Doc);-(Aepa);-Lys-DTyr-D-Tyr-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub> /Doo.Aepa-Lys-DTyr-D-Tyr-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH 2 ^epa}-D-Pha-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys}-Thr-NH

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✓ Doc-Aspa-D-Pha-cydo(Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Cys)-Tir-NH₂ ∠(Doc)<sub>t</sub>-D-Pha-cydo(Cys-(3-lodo-Tyr)-D-Trp-Lya-Val-Cys)-Thr-N**H**<sub>t</sub> ·D-Phe-cydo(Cye-(3-lodo-Tyr)-D-Trp-Lys-Val-Cys)-Thr-NH<sub>2</sub> ∠(Doc)<sub>4</sub>-Aepa-D-Phe-cyclo(Cys-(3-lodo-Tyr)-D-Trp-Lys-Vel-Cys}-Trr-NH<sub>2</sub> /Doc-D-Phe-cyclo[Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Cys]-Thr-NH<sub>2</sub> · (Doc)<sub>2</sub>-Aepa-D-Pha-cyclo(Cya-(3Hodo-Tyr)-D-Trp-Lya-Val-Cys)-Thr-NH<sub>2</sub> ~(Doc),-D-Phe-cyclo(Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Cys)-Thr-NH2 ∠(Doc)<sub>s</sub>-D-Pho-cydo[Cys-(3-lodo-Tyr)-D-Trp-Lys-Val-Cys]-Trr-NH<sub>2</sub>

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/(Doc)<sub>2</sub>-Lya-DTyr-D-Tyr-cyclo[Cya-Tyr-D-Trp-Lya-Abu-Cya]-Thr-NH<sub>2</sub>

/ DooLys-DTyr-D-Tyr-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys}-Thr-NH<sub>2</sub>

(Doc),-Lys-DTyr-D-Tyr-cyclo(Gys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub>

/ (Doc), Lya-DTyr-D-Tyr-cyclo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH,

/(Doc)<sub>8</sub>-Lya-DTyr-D-Tyr-Oydo[Cya-Tyr-D-Trp-Lya-Abu-Cys]-Thr-NH<sub>2</sub> (Doc), Lya-DTyn-D-Tyn-cyclo[Cya-Tyn-D-Trp-Lya-Abu-Cya]-Thr-NH,

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/Dootya-DTyn-D-Tyn-cydo[Cya-Tyn-D-Trp-Lya-Abu-Cya]-Thr-NH<sub>2</sub>

·S (Doc),-Lya-DTyn-DTyn-oydol Cya-Tyn-D-Trp-Lya-Abu-Cyal-Thr-NH<sub>2</sub> O

(Boc), Lya-DTyr-D-Tyr-cyddol Cya-Tyr-D-Trp-Lya-Abu-Cys}-Thr-NH,

S (Doc), Lya-DTyr-D-Tyr-cyclo[Gya-Tyr-D-Trp-Lya-Abu-Cya]-Thr-NH,

(Doc)-Lya-DTyr-D-Tyr-cyclo[Cya-Tyr-D-Trp-Lya-Abu-Cya]-Thr-NH-

(Doc), Lya-DTyr-D-Tyr-cydo[Cya-Tyr-D-Trp-Lya-Abu-Cya]-Thr-NH,

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| | | Aage-Dhel-oydolOye-Tyr-D-Trp-Lys-Vel-Cys|-Thr-NH<sub>2</sub>

Auge D-Phe-cydol Cye-Tyr-D-Trp-Lye-Trr-Cyel-Nel-Niv-

Adpa D-Phe-cydd(Cys-Phe-D-Trp-Lys-Thi-Cys)-Thi-ol

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| | | N | (Doc);^Aapa-D-Phe-cyclo(Cys-Tyr-D-Trp-Lys-Albu-Cys]+Thr-NH

N DOOARDE-D-Phe-cyclo(Cye-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NV4

N AppenDPhecyclo(C)s-Tyr-DTrp-Lys-Abu-Cys)-Thr-NNs

- Phecydoloya-Tyr-D-Trp-Lys-Abu-Cys}-Thr-NH2

N NOODPHOODOLOGY-TW-DTP-Lys-Abu-Cys]-TH-NH-

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(Doo),-Lys-OTyr-D-Tyr-cyclo[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>2</sub> (Doc)<sub>6</sub>-Lya-DTyr-D-Tyr-cydo[Cya-Tyr-D-Trp-Lya-Abu-Cya]-Thr-NH<sub>2</sub> \(\(\)(Doc)\_3-Lya-DTyr-D-Tyr-cydo(Cya-Tyr-D-Trp-Lya-Abu-Cya)-Thr-NH2 \(Doc)\_cLys-DTyr-D-Tyr-cydo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Trr-NH<sub>2</sub>

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Doo-Lys-DTyr-D-Tyr-cydo(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub>

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\apa-Aapa-Lya-D-Tyr-D-Tyr-cydo(Cya-Tyr-D-Trp-Lya-Abu-Cya}-Thr-NH<sub>2</sub>

or a pharmaceutically acceptable salt thereof.

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A compound according to the formula:

— Doc-D-Phe-cydo(Cye-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub>

Ethyl-[6-methyl-8β-ergolinylmethyl]thioacetate;

6-Methyl-8β-ergolinylmethylthioacetyl-D-Phe-c/Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH<sub>2</sub>;
10 Ethyl-(6-n-propyl-8β-ergolinyl)methylthioacetate;

6-n-propyl-8β-ergolinylmelhytthioacetyl-D-Pha-q(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH₂; 6-D-Methyl-8β-ergolinylmethylthiaminosucchoyl-D-Pha-q(Cys-Tyr-D-Trp-Lys-Abu-Cys)-Thr-NH₂;

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CH3/2-N CPHec(C)3-Tyr-D-Trp-Lys-Abu-C)3-Thr-NH3,

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Aepa-D-Phe-cydo[Cys-Tyr-D-Trp-Lys-Abu-Cys]-Thr-NH<sub>2</sub>

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or a pharmaceutically acceptable salt thereof.

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A compound according to the formula:

or a pharmaceutically acceptable salt thereof.

amount of a compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof. thereof, wherein said method comprises administering to said subject an effective -A method of eliciting a dopamine receptor agonist effect in a subject in need

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amount of a compound according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof. thereof, wherein said method comprises administering to said subject an effective A method of eliciting a somatostatin receptor agonist effect in a subject in need

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method comprises administering to said subject an effective amount of a compound and a somatostatin receptor agonist effect in a subject in need thereof, wherein said according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof. A method of simultaneously eliciting both a dopamine receptor agents effect

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pharmaceutically acceptable carrier. according to any one of claims 1-6, or a pharmaceutically acceptable salt thereof, and a A pharmaceutical composition comprising an effective amount of a compound

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15 5 Cushing's Syndrome, gonadotropinoma, hyperparathyroidism, Graves' Disease, pylori proliferation, acromegaly, restenosis, Crohn's disease, systemic sclerosis, according to any one of claims 1-8, wherein said disease is selected from the list melitus, hypertipidemia, insulin insensitivity, Syndrome X, angiopathy, proliferative postprandial hypotension, panic attacks, GH secreting adenomas, Acromegaly, TSH hepatome, leukemia, meningiorna, cancer cachexia, orthostatic hypotension, diarrhea, chemotherapy related diarrhea, scleroderma, irritable Bowel Syndrome, consisting of lung cancer, glioma, anorexia, hypothyroidism, hyperaldosteronism, H. administering to said subject a therapeutically effective amount of a compound 11. A method of treating a disease in a subject, said method comprising secreting adenomas, prolactin secreting adenomas, insulinoma, glucagonoma, diabetes diabetic neuropathy, Paget's disease, polycystic ovary disease, thyroid cancer pancreatitis, small bowel obstruction, gastroesophageal reflux, duodenogastric reflux external and internal pancreatic pseudocysts and ascites, VIPoma, nesidoblastosis, retinopathy, dawn phenomenon, Nephropathy, gastric acid secretion, peptic ulcers hyperinsulinism, gastrinoma, Zollinger-Ellison Syndrome, diarrhea, AIDS related

20 gastrointestinal bleeding, obesity, and opioid overdose. angiogenesis, arthritis, allograft rejection, graft vessel bleeding, portal hypertension diarrhea syndrome, pancreatitis, gastrointestinal hormone secreting tumor enterocutaneous fistula, pancreaticocutaneous fistula, Dumping syndrome, watery

12 The method according to claim 11, wherein said disease or condition is acromegally.

13. A method according to any one of claims 7, 8, 9, 11 or 12, wherein said compound

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or a pharmaceutically acceptable salt thereof.

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14. A pharmaceutical composition according to claim 10, wherein said compound is:

or a pharmaceutically acceptable sait thereof.

- 16. A compound according to claim 1 or 2, wherein z is a molety comprising -H, -OH, (C<sub>1</sub>-C<sub>2</sub>)alkoxy, arylalkoxy, -NH<sub>2</sub>, or -NR9R10;
   or a pharmacoutically accoptable salt thereof.
- A compound according to claim 15, wherein z is a molety comprising -H, -OH,
   (C1-C6)alkoxy, or benzyl;
   or a pharmaceutically acceptable salt thereof.
- 17. A compound according to claim 15, wherein said compound is according to the formula:

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or a pharmaceutically acceptable salt thereof.

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Relevant to claim No. Documentation searched other than minimum documentation to the extent that each documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) International application No. PCT/US02/17859 Date of mailing of the International search report US 4,871,717 A (COY et al) 03 October, 1989, see entire document 1-17 US 4,904,642 A (COY et al) 27 February 1990, see entire 1-17 document. decurrent meruber of the earne patent family Citation of document, with indication, where appropriate, of the relevant passages DAVID LUKTON HALL Telephone No. (703) 308-0196 ording to International Patent Classification (IPC) or to both national classification and IPC FIELDS SEARCHED himm documentation searched (destification system followed by destification symbols) Further documents are listed in the continuation of Box C. INTERNATIONAL SEARCH REPORT C DOCLMENTS CONSIDERED TO BE RELEVANT decurrent published prior to the knowmbornal filing date but later than the priority date claimed Date of the actual completion of the international search A CLASSIFICATION OF SUBJECT MATTER IPQ() :COTK 1/00
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Fracturals No. (TOS) 506-5250
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